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(54) Title: TREATMENT OF ACUTE HEADACHES AND CHRONIC PAIN USING RAPIDLY–CLEARED ANESTHETIC DRUG AT SUB–ANESTHETIC DOSAGES

(57) Abstract

A rapidly–cleared anesthetic drug such as propofol can be used to treat migraine or cluster headaches and other "runaway pain" conditions. When used at a sub–anesthetic dosage level that does not cause a loss of consciousness, propofol (a drug used in surgical anesthesia, which is normally injected but which also can be inhaled) induces a feeling of sedated relaxation. This sedated relaxed condition can interrupt and stop a "runaway pain" condition such as a migraine or cluster headache, as well as various types of intractable chronic pain, such as trigeminal facial pain or arachnoiditis. Typical treatments have used about 2 to 3 ml initially, followed by additional 2–3 ml boluses at timed intervals, depending on the pain status reported by the patient. When a desired level of sedation is reached and the patient reports that the pain is gone, the drug is terminated. It should be rapidly metabolized and eliminated from the blood, so that patients can recover quickly to an alert and functioning state (usually within 10 to 15 minutes, when propofol is used) and can safely drive away from a clinic and return to work or other normal activities, with no unpleasant side–effects or lingering after–effects. In tests on patients suffering acute migraine or cluster headaches or early–onset symptoms of cluster headache, most patients reported 100% relief with no problems of rebound headache the following day. In patients treated for chronic intractable pain, propofol treatment usually provided effective pain relief for about 3 to 5 days before another treatment was needed.

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TREATMENT OF ACUTE HEADACHES AND CHRONIC PAIN USING RAPIDLY-CLEARED ANESTHETIC DRUG AT SUB-ANESTHETIC DOSAGES

BACKGROUND OF THE INVENTION

This invention is in the fields of pharmacology and pain management, and relates to drugs that can stop or reduce pain caused by an acute headache (such as a migraine or cluster headache), or pain of a chronic and intractable type (such as trigeminal facial pain or arachnoiditis).

Migraine headaches (also referred to simply as migraines, for convenience) and cluster headaches are well-known medical conditions. Extensive background information on them is contained in references such as such as *Headache in Clinical Practice* (edited by S. Silberstein et al., Oxford Univ. Press, 1998); *The Headaches*, by J. Olesen; and *Headache Disorders: A Management Guide for Practitioners*, by A. Rapoport and F. Sheftell (W.B. Saunders, Philadelphia, 1996). Various definitions, categories, and diagnostic standards which relate to migraine headaches (and to cluster headaches, described below, and other types of headaches as well) are defined by standardized criteria that were approved and issued by the International Headache Society (IHS), and were published as a supplement to the journal *Cephalalgia* in 1988.

Despite the emergence of the "triptan" drugs, including sumatriptan (sold under trademarks such as IMITREX and IMIGRAN by Glaxo-Wellcome, and also used to treat cluster headaches), naratriptan (sold under the trademarks AMERGE and NARAMIG, also by Glaxo-Wellcome), zolmitriptan (sold under the trademark ZOMIG, by Zeneca Pharmaceuticals), and rizatriptan (sold under the trademark MAXALT, by Merck), there are no adequately safe, rapid, reliable, and satisfactory treatments for recurrent migraines or cluster headaches. The problems and limitations that plague such treatments (and other known treatments) include: (i) patients with various types of cardiac or vascular problems cannot take triptan drugs safely; (ii) significant numbers of patients who repeatedly take any single treatment run a substantial risk of developing a form of tolerance which can lead to elevated chronic and even continuous headaches; (iii) relief often takes well over half an

hour to reach appreciable levels; and (iv) immediately after a treatment, a patient often needs to rest quietly for several hours, which renders it very difficult or impossible for him or her to return to work or get anything else constructive done that day.

Accordingly, a vast medical need exists for improved medical treatments which can provide rapid relief from the intense pain of acute migraine or cluster headaches, and which are not associated with problems of migraine recurrence, lingering sedation, unwanted side effects, or elevated health risks in certain categories of patients.

BACKGROUND ON PROPOFOL AND GABA-A RECEPTORS

Prior to this invention, to the best of the Applicant's knowledge and belief, a drug called "propofol" has never been used to treat acute migraine or cluster headaches. It has been used, instead, as an anesthetic or "pre-anesthetic" agent, in conjunction with surgery.

Since a new and newly-discovered use for propofol plays a key role in this current invention, this section provides background information on what is already known about propofol, and about the use of propofol as an anesthetic.

"Propofol" is the common chemical name for 2,6-diisopropyl-phenol, which is also called 2,6-bis(1-methylethyl)phenol. A specific formulation containing this active agent in an injectable emulsion is sold in ampules and vials by Zeneca Pharmaceuticals (Wilmington, Delaware), under the trademark DIPRIVAN. It is discussed in various texts such as the *Merck Index* and the *Physicians Desk Reference*, and in various published articles cited therein. Additional information on propofol and on the DIPRIVAN formulation is also available via the Internet, at web sites such as www.diprivan.com/PI.html and www.med.umich.edu/anes/drug_profiles/propofol.html.

DIPRIVAN is a potent anesthetic, and it can be used to rapidly render a patient completely unconscious. Indeed, in some clinical tests, it has been used to keep badly burned patients in an essentially comatose state for weeks at a time, while their burns partially heal. However, because DIPRIVAN contains only 10 mg/mL propofol (about 1% on a weight/volume basis), it can be administered intravenously at dosages that can be easily titrated for any particular patient. By simply adjusting a tube-squeezing valve that controls the "drip rate" in standard intravenous tubing, it is not very difficult to establish and sustain a hypnotic and/or profoundly relaxed state without causing a loss of consciousness, using intravenous DIPRIVAN.

Propofol can strongly decrease respiratory activity and blood pressure. Therefore, it

is a potentially dangerous drug which is available by prescription only, and it should be used only in a clinical or hospital setting, under trained care and supervision. Proper equipment and stimulatory drugs (such as norepinephrine) should be immediately available, in case a patient gets too much propofol (or suffers an unexpected adverse reaction to the drug), since it can cause potentially dangerous suppression of respiration or circulation. Preferably, a patient receiving propofol should be continuously connected to one or more monitors (such as heartbeat, blood pressure monitor, and blood oxygen monitors), which should be equipped with alarms that will sound an alert if the patient's respiration or circulation begin to drop to abnormally low levels.

Propofol is known to act as an "agonist" at the "A" subclass of GABA receptors (Hara et al 1993 and 1994; Adodra et al 1995). GABA stands for gamma-amino-butyric acid, which is one of the most important inhibitory neurotransmitters in both the brain and the peripheral nervous systems.

The role of GABA as an inhibitory (rather than excitatory) neurotransmitter must be clearly recognized. Very briefly, when an *excitatory* neurotransmitter molecule (such as glutamate or acetylcholine) is released by a neuron into the liquid in a "synapse" (i.e., a transmitting junction between two neurons), the excitatory neurotransmitter molecule contacts and briefly binds to a receptor protein embedded in the synaptic membrane of the signal-receiving neuron. That brief binding reaction causes one or more ion channels which pass through the neuronal membrane to open up for a few milliseconds. The opening of an ion channel through the membrane of the neuron allows one or more types of ions to flow into and out of the neuron, from the extracellular fluid that surrounds the neuron.

As discussed in any textbook on neurology or physiology, neurons attain a "ready-to-fire" status when they are in a resting state. This "ready to fire" condition is, in a sense, a high-energy plateau, where an electrochemical voltage of about 65 millivolts (in most CNS neurons; up to about 90 millivolts in other types of peripheral neurons) exists across the neuron's outer membrane. A neuron achieves that resting but polarized condition mainly by pumping sodium and calcium ions (which are positively charged) out of the cell. This voltage differential across the cell membrane also tends to draw chloride ions (which are negatively charged) out of the cell, into the positively charged fluid that surrounds the cell.

When excitatory receptors in a synapse are triggered, they open up one or more ion channels across the cell membrane. These ion channels allow ions to flow into and out of

the neuron. If enough channels are opened during a brief span of time, a "depolarizing" event occurs, which is interpreted and processed by the neuron as a "firing" event. The neuron then carries out two functions: (i) it releases some of its own neurotransmitter molecules into other synapses, thereby passing on the nerve signal to other neurons, and (ii) it closes its ion channels and quickly begins pumping ions back across the outer membrane to regain its polarized "ready-to-fire" status again, so it will be ready to receive and process the next arriving nerve impulse.

In contrast to excitatory neurotransmitters, *inhibitory* neurotransmitters (such as GABA) have an opposing effect on neuronal firing. If a molecule of GABA contacts and reacts with a GABA receptor on a neuron, the reaction between the GABA molecule and the GABA receptor causes that neuron to become *less* susceptible to being triggered and fired by excitatory events.

It is generally believed that GABA performs this function by opening (and keeping open, for some period of time) a chloride ion channel which passes through the neuronal membrane. This opening of chloride ion channels alters the polarized status of the neuron, which in turn reduces the ability and readiness of the GABA-inhibited neuron to go through the various steps of a firing (depolarization) event. As a result, even if the "upstream" synapses of a GABA-inhibited neuron are contacted and triggered by excitatory neurotransmitters, the GABA-inhibited neuron will be less ready, and less able, to pass the incoming nerve signal on, to other neurons.

Inhibitory neurotransmitters are extremely important to the functioning of the central and peripheral nervous systems. They can be compared to the tuning components in a radio or television set. If a radio does not have a properly working tuner, and plays any and all signals it receives, the result will be a chaotic, jumbled, uncoordinated mix of dozens of different and competing signals. In order for a radio or television to work properly, it must be able to receive and properly process the signals that are arriving on just one channel at a time, while suppressing and filtering out competing signals from all other channels. In an analogous manner, in order for a brain to be able to process coherent thoughts without constant disruptions and distractions from dozens of other nerve impulses, the brain uses inhibitory neurotransmitters such as GABA to help it filter out and regulate unwanted and distracting nerve impulses.

A number of inhibitory neurotransmitters, such as dopamine and serotonin, have only moderate strength as neuronal inhibitors. Drugs that interact with dopamine or

serotonin receptors tend to be psychoactive drugs; they do not render a patient numb or unconscious, and are used instead for treating various mental states (depression, psychosis, etc.) rather than as sedatives or anesthetics.

By contrast, GABA is a potent inhibitory neurotransmitter, which can inhibit nerve impulses to the point of completely blocking and preventing the transmission of nerve impulses. As such, GABA agonists can be used as sedatives and anesthetics; they can render a patient completely unconscious during surgery. Most of the powerful barbiturates and anesthetics that can render someone totally unconscious are GABA agonists.

As noted above, propofol is known to be a GABA agonist, and it can quickly render someone totally unconscious, in suitable dosages. It is often used as an initial or "pre-anesthetic" agent, to heavily sedate patients who are about to be taken into surgery. After the patient enters the operating room, the use of propofol (which is relatively expensive) is often discontinued, and a gaseous agent such as isoflurane, enflurane, or sevoflurane (which are less expensive than propofol) is usually administered as the main anesthetic drug.

The complete neuronal receptor activity profile of propofol is not fully understood, and it may also have activity at various other types of neuronal receptors; in general, most of the highly effective anesthetics tend to block neuronal activity by means of activity at several classes of receptors, rather than just a single receptor type. However, the only published reports to date on specific receptor activity apparently focus solely on GABA type A receptors, referred to herein as GABA-A receptors.

GABA-A receptors are a complex topic in their own right, and there are multiple subtypes of GABA-A receptors. A typical GABA-A receptor complex is made up of 5 different protein subunits; however, at least 6 different protein subunits have been identified, and different GABA-A receptor subtypes are made up of varying combinations of those subunits. For review articles that describe GABA receptors in detail, see, e.g., Barnard et al 1998, Costa et al 1998, Korpi et al 1997, and Avoli et al 1997.

Various published reports (mostly involving artificial GABA receptors formed from protein subunit combinations that were created in non-GABA cells, using genetic engineering) state that propofol acts at the alpha-1, gamma-2, and beta subunits of GABA-A receptors (Lam et al 1998; Sanna et al 1995a and 1995b), and apparently does not have any particular affinity for other types of gamma or rho subunits of GABA-A receptors (Jones et al 1995). Other reports (e.g., Peduto et al 1991) state that propofol acts at a site within the

GABA-A receptor complex that is distinct from a binding site that interacts with benzodiazepine drugs such as diazepam (sold under the trademark VALIUM).

Recently, it has also been disclosed that propofol can be administered for surgical anesthesia purposes as an inhalable gaseous agent; see US 5,496,537 (Henry 1996), using certain types of hydrofluorocarbon propellants, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. This patent states that since propofol is highly lipophilic, it is readily absorbed into circulating bloodstream through the airway mucosa, leading to rapid onset of anesthesia without the requirement of an intravenous puncture.

It should be noted also that various other types of known GABA-A anesthetics (including isoflurane, enflurane, and sevoflurane) are also volatile gases, which are administered by inhalation rather than intravenous injection.

Accordingly, any such gaseous GABA-A anesthetics (including propofol or its analogs) can be evaluated for potential use as disclosed herein, if desired, to avoid the need for needlesticks when intravenous injection is involved.

It should be recognized that under standard practices for surgical anesthesia, an intravenous line is almost always established before an inhalable gas is used, so that if a patient goes into a severe respiratory or circulatory depression or collapse, the already-established intravenous line can be used immediately for emergency injection of stimulant drugs. However, since the new uses disclosed herein involve "sub-anesthetic" dosages which preferably never cause any loss of consciousness, any attendant risks should be very small. Accordingly, clinical testing is likely to indicate that inhalable administration of sub-anesthetic dosages, to treat severe headaches or other types of acute pain as disclosed herein, can be carried out in complete safety without requiring prior establishment of intravenous access, especially if a rapid emergency medical response is available immediately, under the care of a trained physician, if a particular patient begins to show respiratory or circulatory depression.

Accordingly, one object of this invention is to disclose and provide a method for treating an acute migraine, cluster, or other severe headache, to reduce or entirely stop the pain caused by the headache.

Another object of this invention is to disclose and provide a rapid and highly effective method for treating a migraine, cluster, or other acute headache, in a manner which provides a highly effective treatment with virtually no adverse side effects or lingering after-effects (such as drowsiness, grogginess, disorientation, nausea, or other such

problems), thereby allowing the patient to be ready and able to drive, work, or carry out any other normal activity within an hour after such treatment is commenced.

Another object of this invention is to disclose and provide a method for aborting and preventing migraine, cluster, or other acute headaches, as soon the symptoms of an approaching headache begin to appear in a patient.

Another object of this invention is to disclose and provide a method for treating chronic and/or intractable pain, such as trigeminal facial pain, arachnoiditis, etc.

These and other objects of the invention will become more apparent through the following summary and description of the preferred embodiments.

SUMMARY OF THE INVENTION

A method is disclosed for using a rapidly-cleared anesthetic drug, such as propofol, to treat acute migraine headaches, cluster headaches, and other acute headaches. When administered at sub-anesthetic dosages, by means such as intravenous injection or inhalation, propofol (an anesthetic drug normally used for surgery) can induce a feeling of sedated relaxation without loss of consciousness. This sedated condition can interrupt and effectively stop a "runaway pain" condition such as a migraine or cluster headache. Once the desired level of sedation is reached and the patient reports that the headache is gone, administration is terminated, and the propofol is cleared rapidly from the bloodstream, mainly by enzymatic actions in the liver which allow it to be eliminated via urine. Patients recover quickly to a fully alert and functioning state, usually within 10 to 15 minutes, and can safely drive away from the clinic and return to work or other normal activities, with no unpleasant side-effects or lingering after-effects. In tests on acute migraine and cluster headache patients, most patients reported 100% relief from the acute headache, with no problems of rebound headache the following day.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention discloses a method for using a "rapidly- cleared anesthetic drug" to treat acute migraine headaches, cluster headaches, or other severe headaches, and for treating chronic and/or intractable pain, as discussed below.

As used herein, the phrase "rapidly-cleared anesthetic drug" refers to a drug, such as propofol or a suitable analog thereof, which has both of the following characteristics: (1) it must have a half-life, in circulating blood in typical human patients, of about 30 minutes or less; and (2) it must be pharmacologically acceptable and effective as an anesthetic drug, as that term is conventionally used by physicians and pharmacologists.

As defined in *Stedman's Medical Dictionary*, 26th edition (Williams & Wilkins, Baltimore, 1995), an anesthetic drug is a drug which depresses nerve function, leading to a loss of sensation. In layman's terms, an anesthetic drug is a drug that causes drowsiness, sleepiness, or a similar hypnotic or dissociated mental state, if administered in a manner that causes the drug to reach the brain. Some but not all anesthetic drugs can also cause a localized feeling of numbness or loss of sensation in a particular part of the body (such as a limb or extremity), if administered locally.

Since anesthetic drugs cause a loss of sensation by depressing nerve function,

anesthetic drugs can cause analgesic activity (i.e., pain-reducing activity). However, it should be recognized that "anesthetic" and "analgesic" activities, although overlapping in some respects, are not identical or co-extensive. By way of example, pain-reducing drugs such as aspirin, acetaminophen, and ibuprofen are analgesics (pain-killers), but not anesthetics. As is well-known to physicians and anesthesiologists, anesthesia by itself, even at levels that lead to apparently total unconsciousness of a patient, does not imply an absence of pain. A patient who is under general anesthesia during surgery usually needs to be treated with both an anesthetic, and an analgesic. Use of an anesthetic without accompanying analgesia can lead to highly adverse symptoms such as severe muscle twitching and the release of distress-signalling hormones in the body of the unconscious patient.

The drug known as "propofol", sold as an injectable liquid formulation under the trademark DIPRIVAN by Zeneca Pharmaceuticals (Wilmington, Delaware), falls squarely within the term, "rapidly-cleared anesthetic drug" as used herein, and it was used in all tests described in the Examples. As noted above, the full chemical name of propofol is 2,6-diisopropylphenol; that same chemical is also known as 2,6-bis(1-methylethyl)phenol. The active ingredient propofol is highly oleophilic (hydrophobic), and does not dissolve easily in water; accordingly, the DIPRIVAN formulation is an injectable emulsion. As disclosed in US 5,496,537 (Henry 1996), propofol can also be administered as an inhalable gas, without requiring an intravenous puncture.

As described in Example 1, intravenous injection of DIPRIVAN was tested as a treatment for acute headaches on 53 patients who appeared, seeking medical treatment, at the Anodyne PainCare Clinic in Dallas, Texas, which is run by the Applicant herein, John Claude Krusz, Ph.D., M.D., who specializes in treating acute headaches and other types of chronic and intractable pain. Most of the 53 patients treated with DIPRIVAN had headaches that were diagnosed as migraine headaches, but one patient suffered from cluster headaches instead, as described in Example 2. The tests disclosed in the Examples did not use blinded treatment procedures or untreated control populations; instead, each patient was informed in advance of the proposed treatment, and gave fully informed consent.

The dosages of DIPRIVAN administered to such patients was well within the "sub-anesthetic" range, in which the patient does not lose consciousness. Typically, an initial dosage of 2 to 3 ml was administered as an initial bolus, and the patient then reported orally to the doctor or other attendant on his or her condition and pain status.

Additional sequential boluses of 2 to 3 ml were then administered, until the patient reported satisfactory resolution of the headache pain.

Out of the 53 headache patients that were treated, 43 patients reported complete and total 100% relief from the pain. In addition, patients who were nauseous or vomiting with their headache reported complete relief of nausea. The remaining patients all reported incomplete yet substantial pain relief, usually by means of ranking the pain on a scale of 1 (mild) to 10 (the worst possible pain). Typically, even patients who did not respond with a complete 100% reduction of pain reported that the pain they were suffering had been reduced from an extremely severe level (usually 9 or 10), to a relatively mild level (usually 3 or 4). In such patients, propofol injection usually was terminated at a total dosage of about 20 to 24 ml.

When all such results are averaged together from all 53 headache patients, the average pain reduction was slightly more than 95%. Average total dosages that were given to patients who obtained a 100% reduction in pain were about 10 to 14 ml of DIPRIVAN, typically administered over a span of about 20 to 30 minutes. Average total dosages given to patients who did not reach a 100% reduction were about 20 to 24 ml, typically over a span of about 45 minutes.

All patients were evaluated by the treating physician before they left the clinic, and all of them were deemed to be fully alert and conscious, fully capable of driving themselves away from the clinic, and capable of returning to their work or other normal activities if they so desired. No patient completely lost consciousness during treatment, and there were no serious adverse reactions in any patient treated in this manner.

Additionally and importantly, none of the patients reported a return of a migraine or cluster headache later that day, or the day following their treatment.

As suggested by these dosages and results, this invention preferably does not involve sustained infusion of an anesthetic drug into a patient. Instead, it preferably should involve a relatively brief administration (such as an intravenous injection lasting about 45 minutes or less, or a relatively brief inhalation session) that is done under the care of a physician, nurse, or physician's assistant, in a manner which takes the patient to a point of highly relaxed and essentially pain-free sedation which stops short of unconsciousness or sleep.

Preferably, the physician or assistant should be able to communicate with the patient throughout the entire procedure. The patient yields (usually quite happily) to a sense of relaxation and relief, which is aided and intensified by the fact that an acute migraine

headache or other such pain begins to rapidly disappear as the drug takes over. If and when the pain completely subsides, the infusion is terminated, and the patient will quickly regain full and alert consciousness, usually within about 10 to 15 minutes.

In summary, this invention discloses a method for treating acute headache pain, comprising the following steps: (A) administering, to a patient who is suffering from an acute headache, a rapidly-cleared anesthetic drug (such as propofol, in a suitable injectable or inhalable formulation) which penetrates mammalian blood-brain barriers, agonizes GABA-A neuronal receptors, and has a half-life in circulating blood of about 30 minutes or less, at an effective dosage which induces a relaxed or hypnotic state without causing a loss of consciousness; (B) monitoring the patient's condition to determine when the drug has reduced the acute headache pain to a level that is acceptable to the patient; and, (C) terminating administration of the drug, in a manner which allows the patient to regain alert consciousness without causing the pain to return.

Additionally, this invention discloses a method for preventing emergence of acute headache pain, in a patient who suffers from repetitive acute headaches (such as migraine or cluster headaches) without such treatment. This method of aborting a headache, before it becomes acute, is performed on a patient who is experiencing symptoms which indicate the "onset" (i.e., the approach, emergence, or other development or impending arrival) of acute headache pain, before the pain becomes acute. This method comprises the step of administering to the patient a rapidly-cleared anesthetic drug (such as propofol), at an effective dosage which prevents the onset of acute headache pain.

THE "RUNAWAY HORSE" ANALOGY

The Applicant (a medical doctor) and his assistants who have carried out or witnessed this treatment on people who were suffering from extremely intense and acute migraine headaches usually compare the results of this treatment to stopping a runaway horse, or a runaway train. Although this is merely an analogy, it may help describe and explain the ability of a rapidly-acting, rapidly-cleared anesthetic drug to provide lasting relief from acute pain.

If a horse has been badly spooked and frightened, it will launch into a "panicked gallop" mode, where it tries to get away from something, as fast as possible, by running just as hard as it possibly can.

However, if someone or something can manage to stop a galloping horse, even if

only for a minute or two, the horse will often be willing to simply stop, without starting up again as soon as the restraint is released. This willingness to stop and rest, and to look around and survey the situation instead of immediately trying to launch into another full gallop, is aided and assisted by the fact that the horse is usually quite tired by then, after having run a hard "wind sprint" just a few moments ago.

Similarly, a runaway train has a huge load of inertia, if it is barrelling down a railroad track at top speed. However, if that train can be completely stopped somehow, even for just a moment, all of that inertia disappears. Once it is at rest, stationary, it would take a very large amount of work to get it running fast again.

In an analogous manner, it appears that migraine and cluster headaches (and various other types of acute or intractable pain) are caused or aggravated, in at least some patients, by one or more "runaway" physiological conditions. In one way or another (the details are likely to vary among different patients), a "vicious circle" is commenced, in which an initial triggering factor leads to an initial physiological response (such as release of histamines, interleukins, lymphokines, stress hormones, Substance P, etc., by certain cells or tissues). This physiological response triggers one or more subsequent cellular or physiological responses (such as blood vessel dilation or constriction, inflammation of a particular tissue type, etc.). This secondary adverse response then aggravates and increases the initial mediating physiological response, thereby causing even more histamines, interleukins, lymphokines, stress hormones, and Substance P to be dumped into the system. This makes things even worse, and further aggravates the secondary adverse response. That type of "vicious circle" can turn into an out-of-control cascade, comparable to a rockslide or an avalanche that keeps gaining more and more speed and momentum as it keeps rolling farther and faster down a slope. This out-of-control process can lead to the types of excruciating pain and agony that are all too familiar to people who suffer from acute migraines and cluster headaches, and to others who suffer from acute intractable pain.

However, as that vicious circle begins to race out of control, other physiological responses and processes in the brain and body will begin trying to reestablish control, and to regain a condition known to physicians and biologists as "homeostasis". In general, homeostasis refers to a type of dynamic and adaptive equilibrium which relies heavily on various feedback and control systems, which allows a complex animal with numerous internal organs (all of which must, in a sense, compete against each other for the limited supply of oxygen and nutrients carried by the blood) to remain alive and healthy.

Homeostasis is a dynamic, constantly changing, highly adaptive process in any living animal; it has to be, since the surrounding environment and numerous impinging factors (including the digestive, exercise, and respiratory states of an animal's body, as well as the status of billions of both benevolent and pathogenic microbes that inhabit that animal at any given moment) are constantly changing. The fact that most humans are able to live for 70 years or more, despite the numerous infections, diseases, and injuries that any human suffers over the course of a lifetime, is a remarkable and even awesome tribute to the ability of the body (including the brain and nervous system) to sustain homeostasis, even in the face of severe and potentially lethal upsets and assaults.

Accordingly, if a migraine headache is likened to a runaway horse which has launched itself into an out-of-control panicked gallop, the brain and body will begin attempting to exert control over that runaway condition, trying to bring it back under control. The brain and body will begin trying to reestablish that type of control, on their own, using natural feedback mechanisms, before any drug intervention is commenced.

Accordingly, treatment with a rapid-acting and rapidly- cleared anesthetic drug, such as propofol or a suitable analog thereof, can provide a potent method for, in effect, lassoing and stopping a runaway horse, for a few minutes. This intervention, which forces the runaway horse to stop for a while, allows the regulatory mechanisms of the brain and body (which have already been fully switched on, by the onset of acute pain from a migraine headache) to respond in whatever way is necessary for them to reestablish control. Those mechanisms can then reestablish full and proper control of the system, in a manner similar to a skilled horse trainer who knows how to calm down and control a tired horse.

The analogy of a runaway horse is just an analogy, and its limitations must be recognized. Nevertheless, that analogy becomes evident and obvious to anyone who has witnessed the medical treatment disclosed herein, and to any patient who has received this type of treatment while suffering from a severe and acute migraine headache.

OTHER CANDIDATE ANESTHETICS; ANALOGS OF PROPOFOL

As disclosed above, this invention involves the use of "rapidly-cleared anesthetic drugs" to treat acute migraine headaches, cluster headaches, or other severe headaches. Although propofol, in an injectable formulation such as DIPRIVAN, appears to have an ideal combination of properties and activities for such use, this invention is not limited to the use of propofol, or of the DIPRIVAN formulation.

For example, various analogs and congeners of propofol are known to have anesthetic properties. A number of such analogs and congeners are listed and described in Trapani et al 1998. Any such analog, congener, isomer, or derivative of propofol which is pharmacologically acceptable, and which has anesthetic properties, can be evaluated for use as described herein, using no more than routine experimentation.

Other salts, isomers, analogs, and derivatives which are not listed in Trapani et al 1998 can also be tested for use as disclosed herein, provided that such salts, isomers, analogs, or derivatives are: (1) pharmacologically acceptable; (2) functionally effective as anesthetic drugs which act as agonists at GABA-A receptors; and (3) rapidly cleared from circulating blood, with a half life of about 30 minutes or less in circulating blood.

For example, a halogen atom might be used instead of the hydroxy group, in the phenol precursor; such compounds were not tested by Trapani et al. As is well-known to chemists, certain types of substituents, when coupled to benzene rings, act as "ortho, para-directing groups" that cause additional substitution reactions to predominately or exclusive involve the "ortho" and "para" carbon atoms in the benzene ring. By way of illustration, if a hydroxy group is bonded to the #1 carbon atom in a benzene ring (thereby constituting phenol as the starting reagent), its electronegative characteristics tend to cause additional substituents (such as isopropyl groups) to bond to the #2 and #6 carbon atoms, which flank the #1 carbon atom; these are the two "ortho" positions. At the same time, the phenol group also minimizes attachment of any new groups to either of the "meta" carbon atoms (i.e., the atoms in the #3 and #5 positions). This effectively reduces the costs of synthesizing propofol in commercial quantities; however, because of steric hindrance by the two flanking isopropyl groups, it is unlikely that the hydroxy group plays an important role in the pharmacological activities of the final compound. Accordingly, various alternate types of atoms or groups are also likely to be suitable as ortho-directing groups, in place of the hydroxy group contained in propofol.

As another alternative approach to creating analogs of propofol, isobutyl groups or larger branched alkyl groups might be used in place of either or both of the isopropyl groups coupled to the benzene ring.

However, it should be emphasized that development and testing of new or additional analogs of propofol are not necessary to this invention, in any way, since propofol appears to be ideally suited for use as disclosed herein.

As used herein, the term "pharmacologically acceptable" embraces those

characteristics which make a drug suitable and practical for administration to humans. For example, such compounds must be sufficiently chemically stable under reasonable storage conditions to have an adequate shelf life, and they must be physiologically acceptable when introduced into the body by a suitable route of administration.

The term "analog" is used herein in the conventional pharmaceutical sense, to refer to a molecule that structurally resembles a referent molecule (2,6-diisopropylphenol, in this case) but which has been modified in a targeted and controlled manner to replace a specific substituent of the referent molecule with an alternate substituent.

The term "derivative" as used herein refers to a molecule that is obtained by using 2,6-diisopropylphenol as a starting compound, and then modifying it in a controlled manner which generates a compound that has the desired traits of a pharmacologically acceptable anesthetic drug which is rapidly cleared from circulating blood.

Administration of the compounds of this invention can use any acceptable technique that is capable of introducing the compounds into the bloodstream. Intravenous injection is currently the standard method of administration, since the only formulations of propofol that have been fully approved for human use are injectable emulsions. However, as noted above and as disclosed in more detail in US 5,496,537 (Henry 1996), propofol also appears to be well-suited for administration as an inhalable gas.

If desired, various propellants other than the fluorocarbons listed in US 5,496,537 can also be evaluated, if desired. For example, a second type of volatile anesthetic called cyclopropane may be useful as both a propellant and an adjunctive anesthetic, for the purposes disclosed herein. Since cyclopropane is highly flammable and potentially explosive, it cannot be used in conjunction with electrical cautery, and it has therefore has fallen into disfavor as an anesthetic during surgery, since cautery is so widely used. However, since treatment of acute headaches or other pain as disclosed herein will not involve cautery in any way, and will not require other equipment that poses a risk of sparking or other ignition, cyclopropane might be useful as a propellant and/or adjunctive agent for propofol or other gaseous anesthetics, for use as disclosed herein.

Accordingly, this invention discloses a composition of matter, comprising an inhalable gaseous mixture containing (i) a first anesthetic drug selected from the group consisting of propofol, and salts, isomers, analogs, and derivatives of propofol which are pharmacologically acceptable as inhalable anesthetic agents, and (ii) a second anesthetic drug comprising cyclopropane, wherein the first and second anesthetic drugs are present in

the inhalable gaseous mixture at therapeutically effective concentrations which allow the inhalable gaseous mixture to be used in inhalant form to treat acute headache pain without rendering a patient unconscious.

This invention also discloses an article of manufacture, comprising (a) a container for holding a pressurized inhalable gaseous mixture, (b) a pressurized inhalable gaseous mixture contained within such container; and (c) outlet means which enable administration of the gaseous mixture to a human patient, wherein the gaseous mixture comprises (i) a first anesthetic drug selected from the group consisting of propofol, and salts, isomers, analogs, and derivatives of propofol which are pharmacologically acceptable as inhalable anesthetic agents, and (ii) a second anesthetic drug comprising cyclopropane, and wherein the container and outlet means act together to allow the gaseous mixture to be used to treat acute headache pain in a human patient without rendering the patient unconscious.

In addition to propofol and its analogs, various other agents are known to act as anesthetics, and most such anesthetics usually have some level of agonist activity at GABA-A receptors; such drugs include volatile gases (such as isoflurane, enflurane, and sevoflurane; see, e.g., Krasowski et al 1998) and various barbiturate drugs (see, e.g., Davies et al 1998). Any such anesthetic drug which has a relatively short half-life (such as about 30 minutes or less; drugs having a half life of about 10 minutes or less are preferred) in circulating blood can be evaluated for use as a treatment for acute headaches, using the methods disclosed herein, with no more than routine experimentation.

If a volatile gas anesthetic is evaluated for potential use as disclosed herein, to determine whether it can be used safely without requiring an intravenous needlestick, it should be recognized that under standard anesthetic practices, an intravenous line is almost always established before an inhalable gas is used. This is a standard safety precaution, so that if a patient goes into a severe respiratory or circulatory depression or collapse, the already-established intravenous line can be used immediately for emergency injection of stimulant drugs. However, testing may indicate that relatively low sub-anesthetic concentrations and/or dosages may be used safely without requiring an intravenous line as a routine precaution, so long as emergency treatment is immediately available if it becomes necessary.

As noted above, rapidly-cleared anesthetic drugs can be used to treat any type of acute headache, either after the headache has emerged in full and acute form, or at any time after one or more "early onset" symptoms begin to arise. Such agents can be used alone or

in combination, in concentrations and dosages that can be evaluated for any type or severity of headache, using no more than routine experimentation, guided throughout the course of treatment of any particular patient by the spoken comments of the patient, who can provide a continuous status report on the progress of the treatment, without ever losing consciousness.

VIALS WITH "SUB-ANESTHETIC" DOSAGES FOR TREATING HEADACHES

This invention also discloses an article of manufacture, comprising a vial which contains a sterile quantity of propofol (or another suitable rapidly-cleared anesthetic drug) which is not sufficient for surgical anesthesia, but which is well-suited for treating a migraine or cluster headache.

Vials of DIPRIVAN that are sold for surgical anesthesia contain 20 ml of the injectable emulsion. Each ml of emulsion contains 10 mg of propofol; accordingly, a vial that has been manufactured for surgical anesthesia purposes contains 200 mg of propofol. That is roughly twice as much propofol as is necessary to treat, quite adequately, a large majority of acute migraine and cluster headaches. Based on the results of tests involving 45 patients, as disclosed in Example 1, it appears that about 80% of all such headaches were fully resolved (i.e., 100% pain relief) by administration of 100 mg or less of propofol (i.e., using only half the surgical dosage of propofol). About 95% of all such headaches were fully resolved (with 100% pain relief) when slightly higher quantities (up to about 140 mg propofol) were administered.

In light of those results, this invention discloses and claims vials that contain a total quantity of a rapidly-cleared anesthetic drug (such as propofol or a suitable analog thereof), in a "sub-anesthetic dosage" (i.e., a dosage which is not adequate to establish complete surgical anesthesia, but which is adequate for providing complete relief from pain in at least 95% of treated patients suffering from acute migraine headache). In one preferred embodiment, this "sub-anesthetic" dosage covers a vial or ampule containing about 100 mg up to about 150 mg propofol.

By reducing the amount of propofol in such vials (such as by reducing the quantity of emulsion, by reducing the concentration of propofol in the emulsion, or by using a completely different formulation), the cost of vials for treating headaches can be reduced compared to the costs of vials with a full 200 mg, as used for surgical anesthesia. To the best of the Applicant's knowledge and belief, vials containing "sub-anesthetic dosages"

(about 100 to 150 mg) of propofol have never previously been manufactured and sold.

TREATMENT OF CHRONIC, INTRACTABLE, OR NEUROPATHIC PAIN

Treatment using a rapidly-cleared anesthetic drug (such as propofol), in a manner as disclosed above, can also be highly useful for treating at least some types of chronic pain that is refractory and/or intractable (i.e., which does not respond adequately to other types of treatment). Tests using propofol to treat trigeminal pain facial or arachnoiditis, with highly successful outcomes, are described in Example 3 and 4.

Other types of chronic refractory and/or intractable pain that are likely to be relieved substantially in at least some patients include (1) phantom limb pain suffered by an amputee; (2) a condition known to physicians as "complex regional pain syndrome"; (3) post-operative pain that has persisted for longer than a month following a surgical operation; (4) pain caused by herpes zoster viruses, in a condition widely known as shingles; and (5) pain caused by certain types of bone degenerative diseases.

It also is recognized by the Applicant that a combined treatment regimen using a rapidly-cleared anesthetic such as propofol is likely to offer an improved treatment for neuropathic pain in many patients. In general, "neuropathic" pain refers to pain that is not adequately blocked by opiate-type drugs. The improved treatment contemplated by the Applicant uses both: (i) initial treatment (and possibly periodic and/or as-needed treatment) with a rapidly-cleared anesthetic drug such as propofol; and, (ii) daily or other chronic treatment using other drugs, such as carbamazepine (TEGRETOL™), gabapentin (NEURONTIN™), amitriptyline (ELAVIL™), topiramate (TOPAMAX™), lamotrigine (LAMICTAL™), or tiagabine (GABITRIL™), or a drug that suppresses activity at the NMDA class of glutamate receptors. Use of NMDA antagonist drugs for treating neuropathic pain is discussed in various patents and other publications; see, e.g., US patents US 5,605,911 (Olney 1997), and 5,629,307 (Olney 1997). Long-term treatment of a chronic and intractable pain condition, using drugs such as these, may be substantially improved if a rapid-acting anesthetic drug such as propofol is used first, at subanesthetic doses, to provide immediate short-term relief from the pain. This would, in effect, allow a chronically administered drug to start from a "ground zero" condition, instead of having to first treat an acute pain condition and then provide lasting relief.

FORMULATIONS AND MODES OF ADMINISTRATION

This invention also contemplates the use of modified injectable formulations which may be preferred for repeated injections of propofol. The current emulsified formulation reportedly contains, in addition to propofol as the active agent, soybean oil (100 mg/mL), glycerol (22.5 mg/mL), and egg lecithin (12 mg/mL), with sodium hydroxide to adjust pH (*Physicians Desk Reference*, 50th Edition, 1996). Recently, disodium edetate has been added to the formulation, to retard the risk of microbial growth. Other efforts are also being made to develop and test other types of preservatives as well.

In at least some patients, the standard emulsified formulation reportedly can cause pain at the site of injection, in at least some patients (e.g., Tan et al 1998; Uda et al 1998; Ozturk et al 1998). In order to avoid or minimize such problems, many physicians have adopted a practice of mixing a small quantity of lidocaine in with the DIPRIVAN formulation, so that both the DIPRIVAN and the lidocaine are mixed together in a saline carrier solution. In addition, it should be recognized that a person who suffers from frequent migraine or cluster headaches may receive a much higher number of propofol injections than someone who is only injected a few times during his/her lifetime, in conjunction with surgery. In the case of a person receiving a large number of injections over the course of a lifetime, it should be recognized that an injected formulation containing a soy product and an egg product may raise a concern over a possible allergic response.

Accordingly, this invention contemplates the use of modified formulations for injection which may not contain various components that are present in the standard DIPRIVAN formulation (such as soybean oil or egg lecithin), and which may pose a lower risk of causing pain at the injection site. Presumably, any such formulation would be likely to contain water, and would likely be in the form of an emulsion, since propofol is strongly oleophilic. One or more synthetic organic compounds having a plurality of hydroxyl groups can be used as an emulsifying agent; various compounds such as propylene glycol, polypropylene glycol, ethylene glycol, polyethylene glycol, dextran compounds, and/or cyclodextrin compounds are often used in such formulations. A buffering or neutralizing compound, and possibly an antimicrobial agent, can also be used in such a formulation.

Alternately, as noted above, any problems that accompany intravenous injection of propofol can likely be avoided by development of one or more formulations that can be administered by means other than intravenous injection. One such class of formulations includes inhalable gaseous formulations, as disclosed in US 5,496,537 (Henry, 1996).

Another alternative delivery system that might be effective for administering suitable

sub-anesthetic dosages of a drug such as propofol involves transdermal delivery systems, such as skin patches. Transdermal delivery systems can use any of a number of known permeable polymers, porous fabrics, or other suitable materials that can release suitable quantities of a drug; one example of such a polymer is disclosed in US patent 4,563,184 (Korol 1986). The quantity of such a drug which reaches and enters circulating blood via a transdermal delivery mode can also be increased by various means, such as (i) by applying heat to the patch, such as by using a heating pad, a compress soaked in hot water, etc., and/or by mixing the pain-reducing drug with a carrier agent that enhances permeation and delivery, such as dimethyl sulfoxide (DMSO).

Still other known modes of administration also can be evaluated for use as disclosed herein; such modes include rectal suppositories, troches, etc.

It should also be noted that two or more modes of administration can be used in conjunction with each other, to treat acute headaches or other forms of acute pain. For example, a patient suffering from frequent (such as daily) cluster headaches could be treated by using an injectable or inhalable formulation in an initial treatment, followed by a skin patch, rectal suppository, or other delivery mode that can continue to release a drug over a period of 48 to 72 hours.

EXAMPLES

Example 1: Treatment of Acute Migraine Headaches

Intravenous injection of DIPRIVAN (an injectable emulsion containing 1% w/v propofol) was used to treat acute headaches on 53 patients who appeared, seeking medical treatment, at the Anodyne PainCare Clinic (Dallas, Texas). Nearly all of these patients had headaches that were diagnosed as migraine headaches by the treating physician; one such patient suffered from a cluster headache, as described in Example 2.

These treatments did not use blinded testing procedures or untreated control populations; instead, each patient was informed in advance of the proposed treatment, and gave fully informed consent.

An initial dosage of 2 to 3 ml was administered, then the patient reported orally to the doctor or attendant on his or her condition and pain status. Additional sequential boluses of 2 to 3 ml were then administered, until the patient reported satisfactory resolution of the headache pain.

Out of the 53 headache patients that were treated, 43 patients reported complete and total 100% relief from the pain. The average total dosages that were given to patients who obtained a 100% reduction in pain was about 100 to 140 mg of DIPRIVAN, typically administered over a span of about 20 to 30 minutes.

All other patients also reported substantial pain relief. When they ranked their pain on a scale of 1 (mild) to 10 (the worst possible pain), those patients who did not obtain a 100% reduction of pain reported that the pain they were suffering had been reduced from an extremely severe level (usually 9 or 10), to a relatively mild level (usually 3 or 4). In such patients, propofol injection was terminated when a total dosage of about 200 to 240 mg was reached; this termination was usually motivated by a desire to avoid any potential adverse consequences (such as respiratory or circulatory depression) that might have been triggered if the patient completely lost consciousness.

When all such results are averaged together, from all 53 headache patients, the average percentage of pain reduction was 95.1%. No patient completely lost consciousness during treatment, and there were no serious adverse reactions in any of the patients treated in this manner. 85% of patients also presented with nausea along with their headache. After propofol treatment all patients described complete resolution of their nausea.

All patients were evaluated by the treating physician, before they left the clinic, and all of them were deemed to be fully alert and conscious, and fully capable of driving themselves away from the clinic, so that they could return to their work or other normal activities.

None of the patients reported a return of a migraine or cluster headache that day, or the day following their treatment.

Example 2: Treatment of Cluster Headaches

One patient who was treated as described above suffered from severe and acute cluster headaches, which usually occurred at a frequency of 2 or 3 headaches per day when such a cluster was in progress. This patient could easily determine when a cluster headache was approaching, usually about 15 to 30 minutes before the onset of a full-blown acute headache.

When he appeared at the clinic, seeking treatment for an oncoming acute headache, he was treated with DIPRIVAN as described above. That treatment totally aborted and prevented his headache, and he went home. He did not report the return of a headache the

following day.

The same patient was subsequently treated with propofol on several additional occasions, when he began to experience the symptoms of an oncoming cluster headache. Each treatment led to generally the same outcome as described above, and was regarded as successful by both the patient and the treating physician.

Example 3: Treatment of Trigeminal Pain

Two patients were treated for chronic and intractable pain involving the trigeminal nerve, a facial nerve which occasionally becomes a locus or focal point for severe facial pain. Trigeminal pain is widely regarded as one of the most difficult forms of pain to treat effectively without putting a patient into a heavily drugged state using a powerful narcotic or barbiturate drug.

Both patients with trigeminal pain were treated essentially as described above, using repeated small (usually 2 to 3 ml) bolus injections of DIPRIVAN, followed by a subsequent oral report from the patient to the attending physician on the severity of the pain, before another small bolus was administered. Each patient eventually received a total of about 20 to 24 ml of DIPRIVAN, over a span of about 45 minutes.

Neither patient reported 100% relief from their trigeminal pain; however, both patients reported a substantial reduction in their pain (roughly a 50% reduction in each case), which brought it down to a tolerable level that allowed them to carry on their normal daily activities.

Both patients also reported that the reduction in pain persisted for a substantial period, which averaged about 2 to 3 days per treatment. No problems suggesting tolerance or addiction were observed by the treating physician.

Example 4: Treatment of Arachnoiditis

A patient who had received a series of back surgeries following a severe automobile accident was diagnosed by the Applicant as suffering from arachnoiditis. The patient was treated using small bolus injections of DIPRIVAN, as described above, and reported nearly 100% pain reduction, which was better than he had ever received before, from any other type of medication.

The initial treatment gave him excellent pain relief for several days, but the chronic pain began to return after about 3 or 4 days. Eventually, over a period of several months,

he settled into a pattern of appearing at the clinic roughly once every 5 days for another injection. On one occasion, he received an injection shortly before taking an out-of-town trip, so that he would feel better during the trip. That was significant, since it was the first out-of-town trip he had felt able to cope with in years. He regarded these treatments as the best source of relief he had ever found from his chronic intractable pain.

Thus, there has been shown and described a new and useful treatment for recurrent acute headaches, such as migraine or cluster headaches, and for chronic intractable pain. Although this invention has been exemplified for purposes of illustration and description by reference to certain specific embodiments, it will be apparent to those skilled in the art that various modifications, alterations, and equivalents of the illustrated examples are possible. Any such changes which derive directly from the teachings herein, and which do not depart from the spirit and scope of the invention, are deemed to be covered by this invention.

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CLAIMS

1. A method for treating acute headache pain, comprising the following steps:

a. administering to a patient suffering from acute headache pain a rapidly-cleared anesthetic drug which:

(i) penetrates mammalian blood-brain barriers;

(ii) agonizes GABA-A neuronal receptors; and,

(iii) has a half-life of about 30 minutes or less in circulating blood,

at an effective dosage which induces a relaxed or hypnotic state of consciousness in the patient;

b. monitoring the patient's condition to determine when the anesthetic drug has reduced the acute headache pain to a level that is acceptable to the patient; and,

c. terminating administration of the anesthetic drug in a manner which allows the patient to regain alert consciousness without causing the pain to return.

2. The method of Claim 1 wherein the anesthetic drug contains an active agent selected from the group consisting of 2,6-diisopropyl-phenol and salts, isomers, analogs, and derivatives of 2,6-diisopropyl-phenol.

3. The method of Claim 1 wherein the acute headache pain is caused by a migraine headache.

4. The method of Claim 1 wherein the acute headache pain is caused by a cluster headache.

5. The method of Claim 1 wherein the anesthetic drug is administered by intravenous injection.

6. The method of Claim 1 wherein the anesthetic drug is administered by inhalation.

7. The method of Claim 1 wherein the anesthetic drug is administered by means selected from the group consisting of transdermal patches, rectal suppositories, and troches.

8. A method for treating acute headache pain, comprising the steps of:

a. intravenously injecting, into a patient suffering from acute headache pain, an anesthetic formulation containing a rapidly-cleared anesthetic drug at an effective dosage which relieves headache pain without causing a loss of consciousness in the patient;

b. monitoring the patient's condition to determine when the anesthetic formulation has reduced the acute headache pain to a level that is acceptable to the patient; and,

c. terminating injection of the anesthetic formulation, thereby allowing the patient to regain alert consciousness.

9. The method of Claim 8 wherein the anesthetic drug contains an active agent selected from the group consisting of 2,6-diisopropyl-phenol and salts, isomers, analogs, and derivatives of 2,6-diisopropyl-phenol.

10. The method of Claim 8 wherein the acute headache pain is caused by a migraine headache.

11. The method of Claim 8 wherein the acute headache pain is caused by a cluster headache.

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12. A method for preventing emergence of acute headache pain in a patient who suffers from repetitive acute headaches without such treatment, comprising the step of administering, to a patient who is experiencing symptoms indicating onset of acute headache pain, an anesthetic drug which penetrates mammalian blood-brain barriers and has a half-life in circulating blood of about 30 minutes or less, at an effective dosage which prevents onset of acute headache pain.

13. The method of Claim 12 wherein the anesthetic drug contains an active agent selected from the group consisting of 2,6-diisopropyl-phenol and salts, isomers, analogs, and derivatives of 2,6-diisopropyl-phenol.

14. The method of Claim 12 wherein the patient has been diagnosed as suffering from migraine headaches.

15. The method of Claim 12 wherein the patient has been diagnosed as suffering from cluster headaches.

16. A method for treating chronic and intractable pain, comprising the following steps:

a. administering to a patient suffering from chronic and intractable pain a rapidly-cleared anesthetic drug which:

(i) penetrates mammalian blood-brain barriers;

(ii) agonizes GABA-A neuronal receptors; and,

(iii) has a half-life in circulating blood of about 30 minutes or less,

at an effective dosage which induces a relaxed or hypnotic state without causing a loss of consciousness in the patient;

b. monitoring the patient's condition to determine when the anesthetic drug has reduced the pain to a level that is acceptable to the patient; and,

c. terminating administration of the anesthetic drug in a manner which allows the patient to regain alert consciousness without causing the pain to return.

17. The method of Claim 16 wherein the anesthetic drug contains 2,6-diisopropyl-phenol as an active agent.

18. The method of Claim 16 wherein the anesthetic drug contains an active agent selected from the group consisting of salts, isomers, analogs, and derivatives of 2,6-diisopropyl-phenol.

19. The method of Claim 16 wherein the chronic and intractable pain falls within by a category selected from the group consisting of trigeminal nerve pain, neuropathic pain, phantom limb pain suffered by an amputee, complex regional pain syndrome, and post-operative pain that has persisted for longer than a month following a surgical operation.

20. The method of Claim 16 wherein the chronic and intractable pain is caused or aggravated by a condition selected from the group consisting of arachnoiditis, herpes zoster viruses, a bone degenerative disease.

21. A method for treating chronic and intractable pain, comprising the steps of:

a. administering to a patient suffering from chronic and intractable pain a rapidly-cleared anesthetic drug which:

(i) penetrates mammalian blood-brain barriers;

(ii) agonizes GABA-A neuronal receptors; and,

(iii) has a half-life in circulating blood of about 30 minutes or less,

at an effective dosage which induces a relaxed or hypnotic state without causing a loss of consciousness in the patient;

b. monitoring the patient's condition to determine when the anesthetic drug has reduced the pain to a level that is acceptable to the patient;

c. terminating administration of the anesthetic drug;

d. subsequently treating the patient with at least one orally-ingested neuroactive drug which is used to treat neuropathic pain.

22. The method of Claim 21 wherein the rapidly-cleared anesthetic drug is selected from the group consisting of 2,6-diisopropyl-phenol, and salts, isomers, analogs, and derivatives of 2,6-diisopropyl-phenol.

23. The method of Claim 21 wherein the orally-ingested neuroactive drug is selected from the group consisting of carbamazepine, gabapentin, amitriptyline, topiramate, lamotrigine, and tiagabine.

24. The method of Claim 21 wherein the orally-ingested neuroactive drug reduces excitation at the NMDA class of glutamate receptors on neurons.

25. An article of manufacture, comprising a sealed vial containing a rapidly-cleared anesthetic drug in a sterile injectable formulation, wherein the vial contains a sub-anesthetic dosage of the anesthetic drug, wherein the sub-anesthetic dosage of the anesthetic drug is inadequate to establish complete surgical anesthesia, but is adequate for providing complete relief from pain in at least two-thirds of treated patients suffering from acute migraine headache.

26. The article of manufacture of claim 25 wherein the rapidly-cleared anesthetic

drug is selected from the group consisting of propofol, and salts, isomers, analogs, isomers, and derivatives of propofol which are pharmacologically acceptable as injectable anesthetic agents.

27. The article of manufacture of claim 25 wherein the sealed vial contains propofol in a dosage range of about 100 mg up to about 150 mg.

28. A composition of matter, comprising an inhalable gaseous mixture containing (i) a first anesthetic drug selected from the group consisting of propofol, and salts, isomers, analogs, and derivatives of propofol which are pharmacologically acceptable as inhalable anesthetic agents, and (ii) a second anesthetic drug comprising cyclopropane, wherein the first and second anesthetic drugs are present in the inhalable gaseous mixture at therapeutically effective concentrations which allow the inhalable gaseous mixture to be used in inhalant form to treat acute headache pain or chronic intractable pain without rendering a patient unconscious.

29. An article of manufacture, comprising:

(a) a container for holding a pressurized inhalable gaseous mixture;

(b) a pressurized inhalable gaseous mixture contained within such container; and,

(c) outlet means which enable administration of the gaseous mixture to a human patient,

wherein the gaseous mixture comprises (i) a first anesthetic drug selected from the group consisting of propofol, and salts, isomers, analogs, and derivatives of propofol which are pharmacologically acceptable as inhalable anesthetic agents, and (ii) a second anesthetic drug comprising cyclopropane,

and wherein the container and outlet means act together to allow the gaseous mixture to be used to treat acute headache pain or chronic intractable pain in a human patient without rendering the patient unconscious.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07232

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A01N 31/08, 37/12, 37/44; A61K 31/05; C07C 39/06

US CL :514/564, 731; 568/781

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/564, 731; 568/781

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, STN (Medline, BIOSIS, CAPlus, Scisearch)
Search terms: propofol, headache, migrane, GABA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,767,117 A (MOSKOWITZ) 16 June 1998 (16/06/98), see entire document, especially columns 3-4.	1-29
Y	WO 96/15782 A1 (THE GENERAL HOSPITAL CORPORATION), 30 May 1996 (30/05/96), see entire document, especially pages 2-5 and 10.	1-29
Y	ZACNY et al. Subjective and Psychomotor Effects of Subanesthetic Doses of Propofol in Healthy Volunteers. Anesthesiology. May 1992, Vol. 76, No. 5, pp. 696-702, see entire article.	1-29

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 19 MAY 2000	Date of mailing of the international search report 05 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MAURIE E. GARCIA Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No. PCT/US00/07232

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HASAN et al. Comparison of the Effects of Propofol and Thiopental on the Pattern of Maximal Electroshock Seizures in the Rat. Pharm. Tox., 1994, Vol. 74, pp. 50-53, see entire article, especially page 52.	1-29
Y	HARA et al. Enhancement by Propofol of the g-Aminobutyric Acid-a response in Dissociated Hippocampal Pyramidal Neurons of the Rat. Anesthesiology. 1994, Vol. 81, No. 4, pp. 988-994, see entire article, especially page 988.	1-29
Y	ADODRA et al. Potentiation, Activation and Blockade of GABA-a Receptors of Clonal Murine Hypothalamic GT1-7 Neurones by Propofol. Br. J. Pharmacology. 1995, Vol. 115, pp. 953-960, see entire article, esepcially the Abstract and the Discussion beginning on page 958.	1-29